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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/659,034	09/09/2003	Hiroaki Shizuya	CIT1620-1	3294

28213 7590 02/25/2008

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EXAMINER	
LI, QIAN JANICE	
ART UNIT	**PAPER NUMBER**
1633	
MAIL DATE	**DELIVERY MODE**
02/25/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/659,034	SHIZUYA, HIROAKI	
	Examiner	Art Unit	
	Q. JANICE LI, M.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-14,16-19,21-25,27-41 and 44-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-14,16-19,21-25,27-41 and 44-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment and response filed 11/27/07 are acknowledged. Claims 1, 7, 8, 16-18, 24, 25, 39-41, 44, 45, 47 have been amended. Claim 43 has been canceled. Claims 1, 3-14, 16-19, 21-25, 27-41, 44-52 are pending and under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated. The arguments would be addressed to the extent it applies to current rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-14, 16-19, 21-25, 27-41, 43-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are vague and indefinite because:

step a of claims 1, 25, 45 requires generating two chimeric DNA constructs comprising human and mouse DNA sequences of the first and second DNA constructs. It is unclear what the chimeric DNA constructs contains beyond one of the 5'- or 3' regulatory sequences.

step b of claims 1, 25, 45 recites, “ligate the ends of the human DNA *comprising* the at least two chimeric DNA constructs". The ends of the human DNA do not comprise the at least two chimeric DNA constructs in the context of the claims. Further, it is unclear where the ends ligate to (e.g. together?), and whether it’s between any random chimeric DNA constructs, such

as two chimeric constructs both contain a 5'- regulatory sequence, and hence the metes and bounds of the claims are uncertain.

Step c of claims 1, 25, 45 recites, recombining the ligated chimeric DNA constructs of step b with the second DNA construct so that the third DNA construct comprises human sequences of the second flanked by mouse sequences of the first DNA. It is unclear how the human sequence in the third construct differs from that of the ligated chimeric DNA construct before it recombines with the second construct again, and hence, the metes and bounds of the claims are uncertain.

Claims 18 and 47 are vague and indefinite because of the claim recitation, "PCR assembled". It is unclear what the phrase means, and embraces in the context of the claims, and thus the metes and bounds of the claims are uncertain.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claim 41 stands rejected under 35 U.S.C. 102(b) as being anticipated by *Shiao et al* (Transgenic Res 1999;8:295-302), and as evidenced by *Wikipedia* Receptor, 2008.

The amended claim 41 deleted the phrase “a metabolic pathway gene”, but still recites "a G-protein coupled receptor gene”. It is noted glucagon receptor is a member of the G-protein coupled receptor family as evidenced by the *Wikipedia*. Accordingly, the following rejection still applies.

Shiao et al teach a transgenic mouse whose genome comprising a genetic construct containing a human glucagon receptor (GR) gene flanked by a first and second mouse DNA sequence orthologous to and have the same order and orientation relative to the human GR gene DNA sequence (See e.g. column 1, page 296, and figure 1a). To the extent that the GR belong to the G-protein coupled receptor family, the mouse disclosed by *Shiao et al* anticipates instant claims.

It is noted that the prior art mouse differs from the instantly claimed mouse only by their method of manufacture. However, patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claims, and a product-by-process claim may be properly rejectable over prior art teaching the same product produced by a different process, if the process of making the product fails to distinguish the two products. *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985).

Accordingly, *Shiao et al* anticipate instant claim.

Claim 41 stands rejected under 35 U.S.C. 102(b) as being anticipated by *Divoky et al*. (Proc. Natl. Acad. Sci. USA 98(3): 986-991, 30 Jan. 2001) and as evidenced by *Wikipedia* Receptor, 2008.

The amended claim 41 deleted the phrase “a cell signaling pathway gene”, but still recites "a kinase gene”. It is noted erythropoietin receptor is a member of the receptor tyrosine kinase family as evidenced by the *Wikipedia*. Accordingly, the following rejection still applies.

Divoky discloses a DNA construct for performing homologous recombination in an ES cell, and a transgenic mouse made from the ES cell. The construct comprises the coding region of the human erythropoietin receptor gene (EPOR) from the start codon to the stop codon flanked by first and second mouse genomic DNA sequences. The first mouse DNA sequence is approximately 7 kb of genomic sequence upstream from the start codon of the mouse EPOR gene, and the second mouse DNA sequence is approximately 5 kb downstream from the stop codon of the mouse EPOR gene, i.e. the portion of the mouse EPOR gene from the start to stop codons has been replaced with its human ortholog. The human EPOR coding sequence comprises a positive selection marker expression cassette (*flox-neo*), inserted within an intron. The recombination events were detected by Southern blotting with an *Eco*RV-*Sal*I 5’ probe and *Xba*I-*Eco*RV 3’ probe, and thus these RE sites are considered as a second selection marker adjacent to one of the non-human DNA sequences. The DNA construct was used to replace the mouse EPOR coding sequence in one copy of the EPOR gene in a mouse ES cell. The modified ES cell-derived blastocysts were then implanted into a pseudopregnant mouse to produce chimeric “humanized” mice which were then bred to produce transgenic humanized mice carrying one or two copies of the human EPOR coding sequence in place of the orthologous mouse EPOR coding sequence. See page 986, col. 2, through page 987, col. 1; page 987, col. 2; Fig. 1, page 988). To the extent that EPOR is a receptor tyrosine kinase (Wikipedia), it meets the limitation of claim 41.

Accordingly, *Divoky et al* anticipate instant claims.

Claim Rejections - 35 USC § 102/103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The prior rejection of Claims 1, 8, 16, 17, 25, 32, 34, 39, 40, 45, 46 under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over *Shiao et al* (Transgenic Res 1999;8:295-302), is withdrawn in view of claim amendment.

The prior rejection of Claims 1, 3, 8, 10, 11, 13, 14, 16, 17, 25, 27, 32, 34, 35, 37, 39, 40, 45 are rejected under 35 U.S.C. 103(a) as obvious over *Divoky et al.* (Proc. Natl. Acad. Sci. USA 98(3): 986-991, 30 Jan. 2001), is withdrawn in view of claim amendment.

Claim Rejections - 35 USC §103

Claims 18, 19, 21-24, 47, 48-52 stand rejected under 35 U.S.C. 103(a) as being obvious over *Divoky et al.* (Proc. Natl. Acad. Sci. USA 98(3): 986-991, 30 Jan. 2001) in view of *Heintz et al* (Nat Rev 2001;2:861-70), and as evidenced by (*Chrast et al*, Transgenic Res 1999 Apr;8:147-50).

Divoky discloses a DNA construct (figure 1) about 20 kb in length, having a structure as described of instant third construct, comprising:

a human DNA coding sequence having at least one intron disposed therein (see the blue fragment in fig. 1C, top row);

A first selection marker gene contained within intron 6 of the human EPOR gene (see neo gene in yellow within the blue fragment);

A first and second mouse DNA sequences flanking the human DNA coding sequence, which are orthologous to and have the same order and orientation relative to the human gene when it is present in the genome of a human (see the fragments in red at the 5' and 3' of the human DNA sequence in fig. 1C).

A second selection marker (PGK/thymidine kinase) is located in the 3' flanking mouse sequence (Xba I site, see fig. 1a). Also *Divoky et al* teach the recombination event was detected by Southern blot with an EcoRV-SalL 5' probe and a Xbal-EcoRV 3' probe, and hence the restriction enzyme sites are second or additional markers adjcent to one of the non-human DNA sequences.

While not explicitly discussed, it was common knowledge in the art that the start and stop codons are usually located at the 5' and 3' flanking sequences respectively for expressing the gene.

Divoky et al also teach introducing the construct to mouse ES cells, and generating genetically modified mouse blastocysts, and subsequently implanting such to pseudopregnant mouse producing a chimeric mouse with "humanized" EPOR gene.

Divoky et al differ from instant claimed in that they used the bacterial artificial chromosome (BAC vector) for carrying the initial wild-type mouse EOPR genome (instant 1st construct), but not the second or third construct as depicted *supra*.

Heintz et al supplemented the deficiency by establishing that at the time of instant filing date, BAC has become the choice of vehicles for genome analysis, and for making targeting vectors to generate transgenic mouse. Compared to other conventional vectors such as YACs, BACs are simple to prepare and manipulate, can carry several hundred kilobases of DNA,

propagated at low copy number, and more stable (e.g. box 1). *Heintz et al* teach the use of reporter genes and targeted-expression have been crucial in the analysis of gene expression and function in many studies including making transgenic animals, but limited in mammalian studies by the intrinsic difficulty of identifying key regulatory elements and large genome manipulation. *Heintz et al* teach the F-factor-based bacterial artificial chromosomes provide a tool that took advantage of the precision of homologous recombination in recombination-deficient strain of *E. coli* (such as a recA mutation, claim 7), which had been used extensively for marker insertion into, and excision from the bacterial genome (e.g. box 1). *Heintz et al* review technical aspects regarding how the BAC works for making target vectors by homologous recombination in the recombination-deficient strain of *E. coli*: a) restoring the capability of homologouse recombination of the BAC by the reintroduction of the *E. coli recA* gene, for example; b) targeting the desired modification cassette into a precise site on the genomic DNA insert using a shuttle vector that carries the desired reporter gene or modification cassette, flanked by sequences homologous to the genomic DNA carried in the BAC; c). using positive and negative selection markers to select correct recombination, to enrich the desired end-product, i.e. a BAC that carries the modification cassette inserted into the exact position chosen in the design of the experiment (e.g. column 1, page 862). *Heintz et al* go on to teach multiple recombination steps might be necessary for resolution or excision. *Heintz et al* also teach the BAC system has been successfully used to insert reporter genes into large segment of CNS-expressed genes and BAC transgenic mice have been made (column 2, page 862).

As to the linearized BAC, it is a mid-product during BAC preparation (*Chrast et al*).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the BAC taught by *Heintz et al,* for carrying the exchange vector as taught by *Divoky et al* with a reasonable expectation of success. The ordinary skilled artisan

would have been motivated to modify the claimed invention because the advantage of the BAC system as taught by *Heintz et al*. Given the levels of the skilled as taught in both cited references, one would have had a reasonable expectation of success for using the BAC carrying the exchange vector. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 41, 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Divoky et al*. (Proc. Natl. Acad. Sci. USA 2001;98(3): 986-991) in view *Xie et al* (Nature 2000;406:435-9, IDS).

Claim 44 is directed to a transgenic mouse whose genome comprising a human drug metabolism gene such as PXR. The teaching of *Divoky et al* as discussed *supra* does not specify such a gene. However, given the desirability for making a humanized xenobiotic response in a mouse model as taught by *Xie et al*, it would have been obvious to one of ordinary skill in the art to apply the method taught by *Divoky et al,* for making a mouse model having a humanized xenobiotic response as taught by *Xie et al* with a reasonable expectation of success. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

In the remarks, the applicant cited second paragraph in col 1, page 862 of Heintz et al, and asserts the method taught by Heintz et al contrast to the instantly claimed invention.

Applicant's arguments have been fully considered but they are not persuasive. This is because the cited paragraph discusses methods *prior to* the discovery of the BAC manipulation method. Further, current rejections are directed to product claims, no longer method claims,

hence, the patentable weight is given to the structure of the products, not how the steps differ that lead to the final construct. Accordingly, the rejections stand.

No claim is allowed. Claims 1, 3-14, 16, 17, 25, 27-40, 45, 46 are free of cited art of record. But they are subject to other rejection/objections.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is **571-272-0730**. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

For all other customer support, please call the USPTO Call Center (UCC) at **800-786-9199**.

/Q. JANICE LI, M.D./
Primary Examiner, Art Unit 1633

Q. Janice Li, M.D.
Primary Examiner
Art Unit 1633

Art Unit: 1633

QJL

February 26, 2008